Supplementary Materials and Methods

Electrophoretic Mobility Shift Assays 1 μM siRNA was incubated with varying molar concentrations of 2xDRBD protein prior to mobility shift analysis as previously described for **Fig. 2** and **Fig. 3**.

Binding of TAT and PPS peptides to HeLa cells Confluent HeLa cells were incubated with 4°C DMEM media containing no peptide or synthetic, N-terminally biotinylated TAT and PPS peptides (American Peptide Company, Inc.) at a concentration of 4 μM for 30 minutes at 4°C. Following incubation, cells were washed twice with 4°C DMEM and then incubated for 20 minutes at 4°C with Alexa-Fluor 488 streptavidin (Molecular Probes) diluted to 4 μg/ml in 4°C DMEM. Cells were then washed three times with Dulbecco's PBS (DPBS) before examination by fluorescence microscopy.White light images were white-balanced and brightness and contrast adjusted equivalently using Adobe Photoshop.

siRNA delivery and HPRT gene silencing *in vitro* Knockdown of HPRT in HeLa cells with Penetratin-2xDRBD was performed as described for **Figs. 4,6, and 7**.

SDS-PAGE and Coomassie staining of purified proteins 0.5 μg or 1 μg of each purified protein was combined with 4x LDS and 10X Reducing Agent Buffer (Life Technologies) and heated at 70°C for 10 minutes. Proteins were electrophoresed on 4-12% NuPagebis-tris gels (Life Technologies) and then stained with SimplyBlue (Life Technologies) Coomassie stain following the manufacturer's protocol. Rainbow RPN 800E (GE Healthcare) andSpectraPlus (Thermo Fisher Scientific) ladders were used for molecular weight determination in **Supplementary Fig.5a** and **5b,c,d**, respectively.